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RESEARCH

Exposure to secondhand smoke and cognitive impairment in non-smokers: national cross sectional study with cotinine measurement

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ABSTRACT

Objective To examine the association between a biomarker of exposure to secondhand smoke (salivary cotinine concentration) and cognitive impairment.

Design Cross sectional analysis of a national population based study.

Setting Stratified random sample of households throughout England.

Participants 4809 non-smoking adults aged 50 years or more from the 1998, 1999, and 2001 waves of the Health Survey for England who also participated in the 2002 wave of the English Longitudinal Study of Ageing and provided saliva samples for cotinine assay and a detailed smoking history.

Main outcome measure Cognitive impairment as defined by the lowest 10% of scores on a battery of neuropsychological tests.

Results Participants who did not smoke, use nicotine products, or have salivary cotinine concentrations of 14.1 ng/ml or more were divided into four equal size groups on the basis of cotinine concentrations. Compared with the lowest fourth of cotinine concentration (0.0-0.1 ng/ml) the odds ratios (95% confidence intervals) for cognitive impairment in the second (0.2-0.3 ng/ml), third (0.4-0.7 ng/ml), and highest fourths (0.8-13.5 ng/ml) were 1.08 (0.78 to 1.48), 1.13 (0.81 to 1.56), and 1.44 (1.07 to 1.94; P for trend 0.02), after adjustment for a wide range of established risk factors for cognitive impairment. A similar pattern of associations was observed for never smokers and former smokers.

Conclusions Exposure to secondhand smoke may be associated with increased odds of cognitive impairment. Prospective nationally representative studies relating biomarkers of exposure to cognitive decline and risk of dementia are needed.

INTRODUCTION

Active smoking may be a risk factor for cognitive impairment and dementia,[1] although it is not clear whether exposure to secondhand smoke is also a risk factor. The health effects of high levels of exposure to secondhand smoke may be close to those of active smoking,[2] including an increased risk of lung cancer, diabetes, cardiovascular disease, hypertension, stroke, and death.[3-9] As the risks associated with secondhand smoke have become clearer, an increasing number of governments have decided to legislate against smoking in public places.[10 11] Given the association between exposure to secondhand smoke and risk factors for cognitive impairment such as cardiovascular disease[4 6] and stroke,[12] it is possible that such exposure may be a preventable risk factor for cognitive impairment. Previous findings also suggest that exposure to secondhand smoke may be associated with poor cognitive performance in children and adolescents.[13-15]

A preliminary analysis of 985 patients (728 women) aged 66-92 years from the Cardiovascular Health Study was carried out (T J Haight et al, 59th annual meeting of the American Academy of Neurology, Boston, 2007) and has been widely reported.[16] Participants who had never smoked, had no history of cardiovascular disease or dementia, and self reported long term exposure to secondhand tobacco smoke (living with a smoker for 30 years or more) were about 30% more likely to develop dementia over a six year period than those who were not exposed (relative hazard 1.3, 95% confidence interval 0.95 to 1.82). This association did not, however, reach statistical significance when adjusted for age, sex, and education (P>0.05). In the same study, participants with subclinical carotid artery disease who lived with a smoker for 30 years or more were more likely to develop dementia (relative hazard 2.38, 1.23 to 4.63), suggesting a potential interaction between exposure to secondhand smoke and subclinical cardiovascular disease. Haight et al therefore hypothesised that exposure to secondhand smoke may be detrimental to cognitive health. Further research incorporating population representative samples while controlling for other factors that may be confounders is needed.

We examined the association between exposure to secondhand smoke and cognitive impairment in a large population based sample of non-smokers.

METHODS

Participants were from the 1998, 1999, and 2001 waves of the Health Survey for England[17] who also participated in

the 2002 wave of the English Longitudinal Study of Ageing.[18] The Health Survey for England is a nationally representative multistage stratified random sample of the community dwelling English population. The core sample of the English Longitudinal Study of Ageing is limited to adults aged 50 years or more in 2002 and is drawn from the Health Survey for England sample by postcode sector (geographical area), stratified by health authority and proportion of households in non-manual socioeconomic groups. Of 11 234 people who took part in both the Health Survey for England and the English Longitudinal Study of Ageing, 8893 were non-smokers at both time points. Cotinine measurements were obtained for most of the eligible non-smoking participants in the Health Survey for England waves 1998 (73%) and 2001 (70%), whereas only a randomly selected subsample of participants received a nurse visit in the 1999 wave and therefore provided a saliva sample (8%). We restricted our analyses to the subsample of 5265 non-smoking participants whose salivary cotinine levels were measured. We excluded 22 participants with a self reported diagnosis of dementia, 205 participants who claimed to be non-smokers but used nicotine products or had salivary cotinine concentrations of 14.1 ng/ml or more (considered to be active smokers),[19] and 229 who had missing values on one or more of the neuropsychological measures used to assess cognitive impairment. The remaining 4809 participants formed the sample for our analyses.

Exposure to secondhand smoke

We used levels of salivary cotinine (ng/ml) measured in the Health Survey for England as a biomarker for recent exposure to secondhand smoke (cotinine is a

Table 1 | Characteristics of non-smoking study population*. Values are numbers (percentages) unless stated otherwise

Variables	All participants (n=4809)	Cognitively normal (n=4328)	Cognitively impaired (n=481)	P for group difference
Exposure to secondhand smoke				
Median (interquartile range)† salivary cotinine (ng/ml)	0.3 (0.1-0.7)	0.3 (0.1-0.7)	0.4 (0.1-1.0)	<0.001
Additional variables				
Mean (SD) age (years)	65.1 (10.3)	63.9 (9.7)	75.5 (9.9)	<0.001
Women	2557 (53)	2288 (53)	269 (56)	0.2
White ethnic origin	4699 (98)	4244 (98)	455 (95)	<0.001
Highest educational qualification:				
None	1810 (38)	1451 (34)	359 (75)	<0.001
Intermediate	1557 (32)	1475 (34)	82 (17)	
Degree or higher	1442 (30)	1402 (32)	40 (8)	
Manual occupational class	1822 (38)	1517 (35)	305 (63)	<0.001
Health Survey for England wave:				
1998	2468 (51)	2201 (51)	267 (56)	0.07
1999	124 (3)	109 (3)	15 (3)	
2001	2217 (46)	2018 (47)	199 (41)	
Median (interquartile range) net non-housing wealth (£)	28 000 (4680-95 000)	31 688 (5600-101 512)	6400 (1500-30 504)	<0.001
Smoking history:				
Never smokers	2014 (42)	1839 (43)	175 (36)	0.03
Former smokers (stopped <10 years ago)	655 (14)	582 (14)	73 (15)	
Former smokers (stopped ≥10 years ago)	2140 (45)	1907 (44)	233 (48)	
Obesity (body mass index >29.9)†	1137 (24)	1025 (24)	112 (23)	0.9
Physical inactivity	497 (10)	377 (9)	120 (25)	<0.001
Alcohol consumption†:				
0 g/day	481 (10)	372 (9)	109 (23)	<0.001
>0-29.9 g/day	3848 (80)	3507 (81)	341 (70)	
≥30 g/day	480 (10)	449 (10)	31 (6)	
Depressive symptoms (CESD >3)	972 (20)	796 (18)	176 (37)	<0.001
Diabetes	320 (7)	259 (6)	61 (13)	<0.001
Cardiovascular disease	601 (13)	484 (11)	117 (24)	<0.001
Stroke	172 (4)	131 (3)	41 (9)	<0.001
Hypertension:				
Untreated	475 (10)	436 (10)	39 (8)	0.001
Treated with antihypertensive drugs	1354 (28)	1183 (27)	171 (36)	

CESD is eight item version of Center for Epidemiological Studies depression scale.[34 35]
*205 participants who claimed to be non-smokers but used nicotine products or had salivary cotinine concentration ≥14.1 ng/ml were considered active smokers and were excluded.[36] 22 patients with a history of dementia were also excluded.
†Variables derived from Health Survey for England. All other variables derived from English Longitudinal Study of Ageing.

metabolite of nicotine that has a half life of around 16-25 hours).[20] Non-stimulated saliva samples were collected according to the Health Survey for England's protocol.[17] Cotinine levels were analysed using a gas chromatograph machine (hp5890; Hewlett Packard, Palo Alto, CA, USA) with a rapid liquid chromatography technique by the Nicotine Laboratory at New Cross Hospital in London.

Cognitive impairment

Cognitive impairment was assessed using neuropsychological tests incorporated in the English Longitudinal Study of Ageing, which are described in detail elsewhere.[21] Briefly, attention and processing speed were assessed using the letter cancellation task from the Medical Research Council National Study of Health and Development.[22] Time orientation was assessed using questions from the mini-mental state examination.[23] Immediate and delayed verbal memory were assessed using a 10-word learning task from the Health and Retirement Study.[24] Prospective memory was assessed by asking participants to remember to write their initials in the top left corner of a piece of paper on a clipboard when it was handed to them later in the session (closely based on a task incorporated in the Medical Research Council Cognitive Function and Ageing Study),[25] and by asking participants to remind the interviewer to record the time when he or she announced that the cognitive section was finished. Numeracy was assessed using questions relating to simple calculations based on everyday situations, and these items have also been incorporated in the Health and Retirement Study.[24] The semantic verbal fluency task was taken from the Cambridge cognitive examination (CAMCOG),[26] which examines how many unique animals people are able to name in one minute.

As the scoring of each individual test varied, we obtained a global cognitive function score by summing the standardised scores on each neuropsychological test. Such composite scores are regularly used because they integrate information from a variety of sources and thus provide a more stable representation of cognitive function than a single test.[27,28] We defined cognitive impairment as the lowest 10% of the distribution of cognitive performance. Such a population based cut-off point is a sensitive and specific marker of cognitive impairment[29] and has been used in previous studies.[30,31]

Statistical analysis

We used multivariable logistic regression models to determine the cross sectional relation between exposure to secondhand smoke and cognitive impairment. We adjusted for key personal and known risk factors for cognitive impairment[32,33]: age, sex, ethnicity, education (highest educational qualification), manual occupational class, fourths of net non-housing wealth (measured in pounds sterling), smoking history (never smokers, former smokers who stopped smoking less than 10 years ago, former smokers who stopped smoking 10 years or more ago), obesity (body mass index >29.9), alcohol consumption (g/day), physical inactivity (participating in sport or physical activity less than once a month), and depressive symptoms (more than three symptoms on the eight item version of the Center for Epidemiological Studies depression scale).[34,35] Variables for adjustment were derived from the English Longitudinal Study of Ageing, with the exception of obesity and alcohol consumption, which were derived from the Health Survey for England.

In a secondary analysis we examined whether any observed association was mediated by a history of medical conditions thought to be associated with smoke inhalation (diabetes, cardiovascular disease, stroke, untreated and treated hypertension).[3-9,12] We analysed former smokers and never smokers separately and investigated whether the same pattern of associations was observed if cognition was operationalised as a continuous variable (global cognitive function) in multivariable linear regression models. In line with the preliminary analysis of Haight et al (59th annual meeting of the American Academy of Neurology) we also investigated the potential interaction between exposure to secondhand smoke and cardio-

Table 2 | Logistic regression models illustrating odds of cognitive impairment (95% confidence intervals) in 4809 non-smokers by salivary cotinine levels

Variable	Basic adjusted model*	Fully adjusted model†	Fully adjusted model plus medical history‡
Salivary cotinine fourths (ng/ml):			
Lowest (0.0-0.1)	Reference	Reference	Reference
Second (0.2-0.3)	1.13 (0.83 to 1.54)	1.08 (0.78 to 1.48)	1.08 (0.79 to 1.48)
Third (0.4-0.7)	1.26 (0.92 to 1.72)	1.13 (0.81 to 1.56)	1.12 (0.81 to 1.56)
Highest (0.8-13.5)	1.68 (1.27 to 2.22)	1.44 (1.07 to 1.94)	1.44 (1.07 to 1.93)
P for trend	<0.001	0.02	0.02

Population weights used to adjust for sampling design.
*Adjusted for age, sex, education, and testing interval.
†Adjusted for age, sex, education, testing interval, ethnicity, manual occupation, net wealth, smoking history, obesity, alcohol consumption, physical inactivity, and depressive symptoms.
‡Adjusted for age, sex, education, testing interval, ethnicity, manual occupation, net wealth, smoking history, obesity, alcohol consumption, physical inactivity, depressive symptoms, history of medical conditions (diabetes, cardiovascular disease, stroke, untreated hypertension, and hypertension treated with antihypertensive drugs).

vascular disease. To take account of potential bias from non-response we used population weights from the English Longitudinal Study of Ageing to make the respondent sample more representative of the population.[18] Non-response to the Health Survey for England and the English Longitudinal Study of Ageing both have the potential to make the respondent sample unrepresentative of the population. We therefore inverted the predicted probability of response for the responding households to provide the initial non-response weight. A further round of weighting was needed to adjust the initial household non-response weight to ensure that the weighted sample of responders closely matched the older English population. In addition, clusters and strata were used to allow for the original complex sample design of the Health Survey for England. We used Stata SE version 9.2 for all analyses (StataCorp, College Station, TX).

RESULTS

Table 1 shows the characteristics of those included in the analysis. Median salivary cotinine levels were low. The patterns of potential confounders observed were in keeping with the general population. The proportion of former smokers who stopped smoking more than 10 years ago was similar to those who never smoked. Most participants consumed alcohol, and about one in 10 were physically inactive. A large proportion of the study population was obese and had significant depressive symptoms or hypertension.

Non-smokers with valid cotinine measurements (n=4809) were similar to the total eligible non-smoking sample from the English Longitudinal Study of Ageing (n=8061) for age (65.1 *v* 65.7 years), sex (53.2% *v* 55.3% women), ethnic origin (97.7% *v* 97.6% white), education (37.6% *v* 40.0% with no qualifications), and occupational class (37.9% *v* 38.6% manual).

Logistic regression was used to determine the relation between exposure to secondhand smoke and cognitive impairment in non-smokers (table 2). Adjustments were made for age, sex, education, and testing interval (basic adjusted models), and then additional covariables (fully adjusted models) were added (see table 2). Those with high levels of salivary cotinine (0.8-13.5 ng/ml) were more likely to be cognitively impaired (odds ratio 1.44, 95% confidence interval 1.07 to 1.94) than those exposed to little or no secondhand smoke (0.0-0.1 ng/ml). Some evidence was found of a linear trend that might indicate a dose-response relation (P=0.02). Additional adjustment for medical conditions such as cardiovascular disease had little effect.

Never smokers exposed to the highest levels of secondhand smoke (salivary cotinine concentrations 0.8-13.5 ng/ml) were more likely to be cognitively impaired (odds ratio 1.70, 1.03 to 2.80) than those exposed to little or no secondhand smoke (0.0-0.1 ng/ml; table 3). Former smokers exposed to the highest levels of secondhand smoke also had increased odds of cognitive impairment (1.32, 0.92 to 1.91), although this association was weaker than that observed for never smokers.

The same pattern of associations was observed when cognitive function was analysed as a continuous variable across fourths of cotinine concentration for both basic models (P for trend <0.001) and fully adjusted models (P for trend 0.025). The introduction of an interaction term to the fully adjusted logistic regression model indicated that there was no statistically significant interaction between history of cardiovascular disease and exposure to secondhand smoke (P>0.2).

DISCUSSION

High levels of salivary cotinine in non-smoking adults may be associated with increased odds of cognitive impairment. A similar pattern of results was observed for never and former smokers, and there was no interaction with a history of cardiovascular disease.

Strengths and limitations

This analysis is to our knowledge the first to examine the relation between exposure to secondhand smoke and cognitive impairment in a large heterogeneous population based sample. We controlled for a wide range of covariables that are potential confounders in cognitive research and incorporated an objective biomarker for exposure to secondhand smoke (salivary cotinine concentration). Comparisons with census

Table 3 | Logistic regression models illustrating odds of cognitive impairment (95% confidence intervals) in former and never smokers by salivary cotinine levels

	Never smokers (n=2014)		Former smokers (n=2795)	
Variable	Basic adjusted model*	Fully adjusted model†	Basic adjusted model*	Fully adjusted model†
Salivary cotinine fourths (ng/ml):				
Lowest (0.0-0.1)	Reference	Reference	Reference	Reference
Second (0.2-0.3)	1.44 (0.90 to 2.31)	1.42 (0.88 to 2.31)	0.95 (0.63 to 1.45)	0.88 (0.57 to 1.34)
Third (0.4-0.7)	1.26 (0.77 to 2.08)	1.16 (0.68 to 1.97)	1.26 (0.85 to 1.86)	1.11 (0.74 to 1.67)
Highest (0.8-13.5)	1.75 (1.10 to 2.78)	1.70 (1.03 to 2.80)	1.62 (1.14 to 2.30)	1.32 (0.92 to 1.91)
P for trend	0.03	0.08	0.005	0.1

Population weights used to adjust for sampling design.
*Adjusted for age, sex, education, and testing interval.
†Adjusted for age, sex, education, testing interval, ethnicity, manual occupation, net wealth, smoking history, obesity, alcohol consumption, physical inactivity, and depressive symptoms.

results show that the sample from the English Longitudinal Study of Ageing has a similar sociodemographic profile to the community living English population.[18]

Several methodological issues should be considered when interpreting our findings. The inclusion of former smokers is potentially problematic as historical exposure may be dominated by the former smoker's own previous smoking behaviours, and misclassification of current smoking status may be particularly likely in this group, leading to a residual confounding effect. We carried out analyses separately for former and never smokers, however, and the association between cotinine levels and cognitive impairment seemed stronger in never smokers. We also adjusted for smoking history as a potential confounder, including number of years since stopping smoking. Furthermore, we excluded 205 participants who claimed to be non-smokers but used nicotine products or had salivary cotinine concentrations of 14.1 ng/ml or more as we considered them to be active smokers.[19] Although cotinine is a valid, sensitive and specific biomarker for recent exposure to secondhand smoke,[37] it does not necessarily reflect exposure over the long period during which cognitive impairment typically develops. However, cotinine levels have proved to be a useful marker of general levels of exposure to secondhand smoke.[37 38] We analysed a series of cross sectional data acquired over a mean of 2.6 years and did not find a causal relation. Although we controlled for a wide range of potential confounders the possibility of residual confounding remains. Non-smokers with valid cotinine measurements had a similar sociodemographic profile to the total non-smoking sample of the English Longitudinal Study of Ageing, and these variables were controlled for in the analyses, making systematic bias unlikely.

Comparison with previous studies

Haight et al (59th annual meeting of the American Academy of Neurology) reported a non-significant trend between self reported exposure to secondhand smoke and risk of incident dementia in never smokers over a six year period. Their sample comprised almost exclusively women, whereas our sample was more heterogeneous. It is possible that their findings were not significant because of the reliance on self reported exposure. Self report measures of secondhand exposure have several important limitations—for example, living with a smoker captures less than half of the variation in cotinine concentration in non-smokers[39] and does not take into account exposure in workplaces and public places. The association we observed between objectively measured cotinine levels and cognitive impairment is consistent with studies suggesting that active smoking may be a risk factor for cognitive impairment and dementia,[1] and that exposure to secondhand smoke is associated with poor cognitive performance in children and adolescents.[13-15]

Possible mechanisms

Several mechanisms have been proposed to explain why exposure to secondhand smoke may increase the odds of cognitive impairment. Exposure to secondhand smoke is associated with an increased risk of cardiovascular disease,[4 6] and cardiovascular disease may in turn be associated with an increased risk of cognitive impairment and dementia.[40 41] While additional adjustment for medical history made little difference to the fully adjusted model, and no interaction between cotinine levels and a history of cardiovascular disease was observed, it is possible that exposure to secondhand smoke may interact with subclinical cardiovascular disease, as observed by Haight et al (59th annual meeting of the American Academy of Neurology). Another study discovered that short term exposure to secondhand smoke adversely affects endothelial function in ways that immediately compromise the cardiovascular system.[42] Dysfunctional endothelial cells contribute to vasoconstriction, atherogenesis, and thrombosis and may therefore compromise the blood supply to the brain. Exposure to secondhand smoke is also a risk factor for incident stroke,[12] and differences in subclinical cerebrovascular disease may help to explain the noticeable individual differences in cognitive function observed during late adulthood.[43] Reverse causality is also possible—for example, participants with cognitive impairment may metabolise nicotine differently from those without cognitive impairment.

Conclusions

Our results suggest that in a large diverse sample of non-smoking adults, high levels of cotinine may be associated with increased odds of cognitive impairment. Given the ongoing international policy debate on exposure to secondhand smoke, this is a topic of major public health significance. Prospective nationally representative studies of the association between biomarkers of exposure to secondhand smoke and cognitive decline and dementia are therefore warranted to assess the relation between secondhand smoke and cognitive health with greater precision. In the meantime, our results provide new evidence to

WHAT IS ALREADY KNOWN ON THIS TOPIC

Active smoking may be a risk factor for cognitive impairment, although it is not clear whether exposure to secondhand smoke is a risk factor

No previous study has examined the association between biomarkers of exposure to secondhand smoke and cognitive impairment

WHAT THIS STUDY ADDS

In a large diverse sample of non-smoking adults, high levels of cotinine were associated with increased odds of cognitive impairment

A similar pattern of results was observed for never and former smokers, and there was no interaction with a history of cardiovascular disease

suggest that exposure to secondhand smoke may be associated with increased odds of cognitive impairment.

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